Remarks

Claims 17, 20, 21, 22, 23, 26-30, 32-33 and 47-51 are pending after entry of the amendments set forth herein. Claim 20 is withdrawn from consideration. Claims 1-16, 18-19, 24-25, 31 and 34-46 are canceled without prejudice. Claims 17, 20, 22 and 26 are amended. Support for these amendments is found in the specification in Table 3, and in the originally filed claims. New claims 47-51 are added. No new matter is added.

The reference in the claims to sequences from Table 3 have been replaced with the specific gene and accession number of the sequences, in order to clarify the intended subject matter. No new matter is added.

Rejections of canceled claims are made moot and will not be further considered.

With respect to the Examiner's rejection of the claims as reciting non-elected subject matter, Applicants note that the restriction has been made final. Applicants therefore attach herewith a petition for review of the restriction requirement.

In response to the sequence election requirement, Applicants note that the present claims are drawn to a method wherein the expression of at least 10 distinct sequences is obtained for analysis, as set forth in Claims 17, 22 and 23; or including expression information from 50 distinct sequences, as set forth in Claims 20, 47 and 48. Such a complex expression profile provides for a robust prediction that is not obtained with profiling of a single sequence.

Applicants respectfully submit that the sequences themselves are not being claimed, as all of the sequences recited in the present application are publicly available and known in the art. Rather, Applicants have provided a means of utilizing information from multiple sequences. As the claims require a minimum of 10 sequences or use of 50 sequences, an election cannot be made of a single sequence.

The difficulties of the Patent Office in searching is understood, however it is respectfully submitted that claims that recite obtaining expression data from at least 10 or 50 sequences are not usefully limited to a single polypeptide or polynucleotide sequence. Applicants respectfully request reconsideration of the restriction.

Rejections Under §102(b)

Claims 1-6, 10-12 and 26-30 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Komarova *et al.* (Oncogene 1998). Claims 1-6 and 10-12 are canceled; Claim 26 has been amended to introduce the limitations of dependent claim 31. In view of the amendments, Applicants respectfully submit that Claims 26-30 are not anticipated by the cited reference. Withdrawal of the rejection is requested.

Rejections Under §103(a)

Claims 17, 18 and 22-25 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gonzalez et al. (USPN 6,015,673) in view of Komarova et al. (Oncogene 1998). Applicants respectfully submit that the present claims are not taught or suggested by the cited art, either for the specific sequences of cyclin B, or for the combined use of at least 10 sequences as set forth in the present claims.

Applicants note that the present claims are drawn to a method wherein the expression of at least 10 distinct sequences is obtained for analysis, as set forth in Claims 17, 22 and 23; or including expression information from 50 distinct sequences, as set forth in Claims 20, 47 and 48. Such a complex expression profile provides for a robust prediction that is not obtained with profiling of a single sequence.

The present invention provides methods for predicting whether an individual subjected to anti-proliferative therapy, particularly therapy that results in DNA damage, *e.g.* radiation therapy will be susceptible to toxicity resulting from the therapy. The ability to predict susceptibility to toxicity allows optimization of treatment, and determination of whether on whether to proceed with a specific therapy, and how to optimize dose, choice of treatment, and the like.

The methods of the invention utilize a reference profile from a cell that has been determined to be susceptible to toxicity from the anti-proliferative agent; and utilizes such information in the determination of whether a patient is suitable for radiation therapy or treatment with a particular anti-proliferative agent.

Applicants further note dependent claims added herein which specifically recite the analysis of all top-ranked 50 genes from Table 3; and of the use of shrunken centroid analysis, which features are not taught in the art.

The office action states that Gonzalez teaches a method of predicting whether a patient is susceptible to undesirable toxicity resulting from treatment with radiation, however the action

notes that Gonzalez et al. does not teach either cyclin B, or the set of genes utilized by Applicants, and does not teach the use of radiation, but rather a chemotherapeutic agent.

Applicants respectfully submit that the set of sequences set forth in the present claims, which have been shown to provide a robust profile for determining a susceptible profile is not taught or suggested by the cited art. First, one of skill in the art is not motivated to swap any gene for any other gene in the genome. Second, as discussed above, Applicants utilize a panel of sequences to provide for a robust prediction.

The secondary reference, Komarova *et al.* does not remedy the deficiencies of the primary reference. Komarova et al. describe genetic sequences whose expression is altered in response to irradiation, but do not teach whether such expression is harmful or helpful to a cell, and thus cannot be used in the determination of whether a patient is susceptible to undesirable toxicity resulting from radiation or anti-proliferative therapy.

It is further noted that the specific panels of genes and methods of analysis set forth in Applicants' dependent claims are not taught in the cited art.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention is patentable under 35 U.S.C. 103. Withdrawal of the rejection is requested.

Claim 21 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gonzalez *et al.* (USPN 6,015,673) and Komarova *et al.* (Oncogene 1998) in view of Wahl *et al.* (USPN 6,251,362).

Applicants respectfully submit that Claim 21 is not taught or suggested by Gonzalez *et al.* (USPN 6,015,673) and Komarova *et al.* (Oncogene 1998) as discussed above. Wahl et al. fails to remedy the deficiencies of the primary references, in failing to teach a set of genes whose patterns of expression are useful in the determination of whether a patient is susceptible to undesirable toxicity resulting from radiation or anti-proliferative therapy. It is not disputed that a grade 2 toxicity is known to be undesirable, and such is put forth as an embodiment of interest and is not relied upon for patentability.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention is patentable under 35 U.S.C. 103. Withdrawal of the rejection is requested.

Claims 31-33 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Komarova et al. (Oncogene 1998) and Tibshirani et al. (PNAS, 2002). Applicants respectfully submit that the presently claimed invention is not taught or suggested by the cited art,

While Komarova et al. teach the determination of an expression profile, the specific use of chrunken centroid analysis is not taught or suggested.

Applicants respectfully submit that Tibshirani *et al.* is not available as art to the present application. 35 U.S.C. 102(a) recites "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States". The publication date of Tibshirani *et al.* is May 2002, which is less than one year before Applicants priority date.

35 U.S.C. 102(a) recites that "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent"

The first and last authors of the cited reference, Robert Tibshirani and Gilbert Chu, are inventors of the present application. It is respectfully submitted that the subject matter taught in the reference is not "by others", but is the work of the present inventors.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention is patentable under 35 U.S.C. 103. Withdrawal of the rejection is requested.

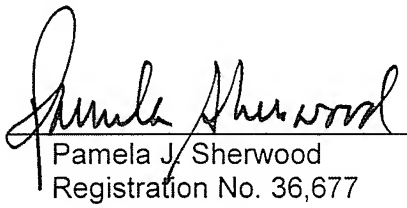
Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-277.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 3, 2007

By: 
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